CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-444/S003

MEDICAL REVIEW(S)

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DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA:	20-444
Document Identification:	SE1-003 AZ; C (Final Safety Update); SE1/BM003
Sponsor:	GlaxoWellcome
Drug name:	FLOLAN (epoprostenol sodium) for Injection
Indication:	treatment of secondary pulmonary hypertension
Date submitted:	October 13, 1999; December 22, 1999; April 28, 1999
Date Received:	October 14, 1999; December 27, 1999; May 3, 1999
Review completed:	March 21, 2000
Reviewer:	Kathy M. Robie-Suh, M.D., Ph.D.

Background:
Flolan is the synthetic sodium salt of epoprostenol (prostacyclin, PGI2, PGX), a prostaglandin vasodilator and inhibitor of platelet aggregation produced mainly in the vascular endothelium. Flolan was approved on 12/20/95 "for the long-term intravenous treatment of primary pulmonary hypertension in NYHA Class III and Class IV patients."

On December 11, 1998 the sponsor submitted an application (S-003) to NDA 20-444 seeking approval of Flolan "for the long-term treatment of pulmonary hypertension due to [redacted] in NYHA Class III and Class IV patients who do not respond adequately to conventional therapy." The application consisted of a single trial in 111 patients having moderate to severe pulmonary hypertension secondary to scleroderma spectrum of diseases and compared conventional treatment to conventional treatment + FLOLAN for a period of 12 weeks. Flolan was given as a continuous intravenous infusion initiated at 2ng/kg/min and increased by 1-2ng/kg/min every 15 minutes or longer until dose-limiting pharmacological effects were obtained or until tolerance to the drug was established. The primary efficacy parameter was exercise capacity as reflected by maximum distance walked during the 6-Minute Walk Test after 12 weeks of study drug treatment. Secondary efficacy parameters included: the 6-Minute Walk Test results at Week 1 and Week 6; cardiopulmonary hemodynamic parameters (mean change from baseline); clinical signs and symptoms of pulmonary hypertension; clinical signs and symptoms of the scleroderma spectrum of diseases as assessed using digital ulcer counts and Raynaud's severity score; and survival over 12 weeks.

The application was found to be inadequate to support the desired indication because:

1. The population studied (patients with pulmonary hypertension due to scleroderma spectrum of diseases) did not adequately reflect the target population (pulmonary hypertension secondary to any cause),

2. Study VA1A4001, as a single trial, failed to adequately support efficacy of Flolan in treatment of secondary pulmonary hypertension.

3. The side effect profile of Flolan in the application reflected its considerable morbidity as outlined in the current product labeling; the available database showed a clearly unfavorable benefit-risk relationship for the use of FLOLAN in treating secondary pulmonary hypertension due to the scleroderma spectrum of diseases.

The sponsor was recommended to conduct an additional controlled clinical trial of Flolan in secondary pulmonary hypertension patients designed to address these concerns.

The sponsor responded to the Not Approvable Letter on August 17, 1999 requesting a meeting to discuss the deficiencies outlined in the Not Approvable letter and to present additional information pertaining to quality of life assessments, mortality and comparability of the primary pulmonary hypertension and secondary pulmonary hypertension clinical studies.

The Division met with the sponsor on September 27, 1999. The Division reiterated that patients from different [redacted] subpopulations differ with regard to clinical manifestations and with regard to underlying disease and etiology of disease and therefore may differ with regard to morbidity and mortality consequences of Flolan use; study of these subpopulations [redacted] would be needed to adequately assess safety of Flolan and evaluate benefit/risk of the drug in these patients.

To provide further support for internal consistency in Study VA1A4001 the Division asked that the sponsor provide a list of patients showing outcomes (including baseline values, values at each timepoint, and the change from baseline) for all primary and secondary endpoints for each patient as well as any summary tables and descriptive statistics necessary to support both correlation among the efficacy endpoints and internal consistency over time.

In the current submission (October 13, 1999) the sponsor includes additional efficacy data tables and listings for patients in Study VA1A4001 and draft labeling for Flolan revised to limit the new indication to pulmonary hypertension (PH) associated with the scleroderma spectrum of disease (SSD). The material is contained in one volume (NDA Vol. 36.1).

The sponsor also has submitted a Final Safety Update (12/22/99) covering the time period from January 1, 1999 through September 15, 1999.

Summary of Additional Efficacy Information for Study VA1A4001:
A total of 111 patients (55 conventional therapy; 56 Flolan) were enrolled and received study medication in Study VA1A4001. The primary efficacy endpoint was maximum distance walked in meters during the 6-minute Walk Test at Week 12. Secondary efficacy parameters included: the 6-minute walk results at Week 1 and Week 6;

cardiopulmonary hemodynamic parameters (mean change from baseline); clinical signs and symptoms of pulmonary hypertension as assessed using the Borg Scale, the Dyspnea-Fatigue Rating and NYHA functional class; clinical signs and symptoms of the scleroderma spectrum of diseases as assessed using digital ulcer counts and Raynaud's severity score; and survival over 12 weeks. In the current submission the sponsor has provided summary efficacy tables for several of these endpoints showing proportions of patients improved or worsened by various amounts over the course of the study. As was discussed in my Medical Officer's Review dated 5/26/99, pages 15 through 21 some patients in both treatment groups were missing data for one or more assessments at one or more of the evaluation times.

At Week 12 among patients having data available, about 72% of Flolan patients as compared to 27% of conventional therapy patients had some improvement or no worsening in 6-minute walk distance as compared to their baseline value. The amount of improvement was greater than 50 meters in about 58% of Flolan patients as compared to 9% of conventional therapy patients. Conversely, more conventional patients than Flolan patients had worsening of 6-minute walk distance at Week 12 as compared to baseline (73% conventional therapy, 28% Flolan), with about 41% of conventional therapy patients showing a decrease of more than 50 meters in distance walked as compared to 18% of Flolan patients. Similar, though less pronounced, results were seen at Week 1 and Week 6 and using other cutoff values for change in walking distance. The sponsor's table summarizing these results is shown below.

Protocol: VA1A40C1
Population: All Subjects, Intent-to-Treat

Table 1
Summary of 6-minute Walk Data

Visit	Treatment	Subjects	Subjects with Walk data	Subjects with a Change in Walk < -50 meters	Subjects with a Change in Walk < -30 meters	Subjects with a Change in Walk < 0 meters	Subjects with a Change in Walk >= 0 meters	Subjects with a Change in Walk > 30 meters	Subjects with a Change in Walk > 50 meters
Week 1	Conventional	55	54	5 (9%)	10 (19%)	32 (59%)	22 (41%)	11 (20%)	6 (11%)
	Flolan	56	50	4 (8%)	10 (20%)	28 (36%)	32 (64%)	19 (38%)	14 (28%)
Week 6	Conventional	55	51	14 (27%)	21 (41%)	30 (59%)	21 (41%)	10 (20%)	8 (16%)
	Flolan	52	48	5 (10%)	7 (15%)	8 (17%)	40 (83%)	32 (67%)	24 (50%)
Week 12	Conventional	48	44	18 (41%)	24 (55%)	32 (73%)	12 (27%)	5 (11%)	4 (9%)
	Flolan	51	50	9 (18%)	11 (22%)	14 (28%)	36 (72%)	30 (60%)	29 (58%)

Similar results were seen for the hemodynamic data where more Flolan patients than conventional therapy patients showed improvement (or no worsening) in cardiac index, cardiac output, pulmonary capillary wedge pressure (PCWP), and oxygen saturation (SaO_2) and other parameters. Fewer Flolan than conventional therapy patients showed worsening with regard to these parameters. The sponsor's table summarizing this data is shown below.

Protocol: VA1A4001
Population: All Subjects, Intent-to-Treat

Table 2
Summary of Hemodynamic Data

Parameter	Treatment	Subjects with Parameter Data	Subjects with a Change in Parameter < 2 SD	Subjects with a Change in Parameter < 1 SD	Subjects with a Change in Parameter < 0	Subjects with a Change in Parameter >= 0	Subjects with a Change in Parameter > 1 SD	Subjects with a Change in Parameter > 2 SD
Cardiac Index (L/min/m**2)	Conventional	48	0 (0%)	5 (10%)	29 (60%)	19 (40%)	3 (6%)	2 (4%)
	Flolan	50	0 (0%)	0 (0%)	10 (20%)	40 (80%)	18 (36%)	6 (12%)
Cardiac Output (L/min)	Conventional	48	0 (0%)	5 (10%)	29 (60%)	19 (40%)	4 (8%)	2 (4%)
	Flolan	50	0 (0%)	0 (0%)	10 (20%)	40 (80%)	19 (38%)	4 (8%)
Heart Rate (bpm)	Conventional	48	2 (4%)	5 (10%)	22 (46%)	26 (54%)	4 (8%)	0 (0%)
	Flolan	50	0 (0%)	2 (4%)	18 (36%)	32 (64%)	8 (16%)	2 (4%)
PAPd (mm Hg)	Conventional	48	1 (2%)	4 (8%)	20 (42%)	28 (58%)	6 (13%)	2 (4%)
	Flolan	50	3 (6%)	16 (32%)	37 (74%)	13 (26%)	5 (10%)	0 (0%)
PAPm (mm Hg)	Conventional	48	0 (0%)	5 (10%)	22 (46%)	26 (54%)	5 (10%)	2 (4%)
	Flolan	50	2 (4%)	18 (36%)	38 (76%)	12 (24%)	3 (6%)	1 (2%)
PAPs (mm Hg)	Conventional	48	0 (0%)	5 (10%)	25 (52%)	23 (48%)	6 (13%)	1 (2%)
	Flolan	50	3 (6%)	18 (36%)	41 (82%)	9 (18%)	2 (4%)	0 (0%)
PCWP (mm Hg)	Conventional	46	0 (0%)	3 (7%)	23 (52%)	21 (48%)	7 (16%)	3 (7%)
	Flolan	47	0 (0%)	5 (11%)	21 (45%)	26 (55%)	4 (9%)	2 (4%)
PVR (WU)	Conventional	44	0 (0%)	0 (0%)	18 (41%)	26 (59%)	4 (9%)	1 (2%)
	Flolan	47	6 (13%)	16 (30%)	40 (85%)	7 (15%)	1 (2%)	0 (0%)
RAPm (mm Hg)	Conventional	47	2 (4%)	4 (9%)	16 (34%)	31 (66%)	6 (13%)	0 (0%)
	Flolan	50	2 (4%)	16 (32%)	28 (56%)	22 (44%)	6 (12%)	1 (2%)
SaO2 (%)	Conventional	48	0 (0%)	3 (6%)	26 (54%)	22 (46%)	3 (6%)	1 (2%)
	Flolan	49	2 (4%)	4 (8%)	20 (41%)	29 (59%)	6 (12%)	1 (2%)
SAPd (mm Hg)	Conventional	48	2 (4%)	4 (8%)	20 (42%)	28 (58%)	5 (10%)	2 (4%)
	Flolan	49	5 (10%)	18 (37%)	36 (73%)	13 (27%)	1 (2%)	0 (0%)
SAPm (mm Hg)	Conventional	48	1 (2%)	3 (6%)	26 (54%)	22 (46%)	3 (6%)	2 (4%)
	Flolan	49	8 (16%)	17 (35%)	37 (76%)	12 (24%)	1 (2%)	0 (0%
SAPs (mm Hg)	Conventional	48	1 (2%)	4 (8%)	28 (58%)	20 (42%)	4 (8%)	2 (4%)
	Flolan	49	5 (10%)	14 (29%)	36 (73%)	13 (27%)	3 (6%)	0 (0%)
SVRI (%)	Conventional	44	0 (0%)	6 (14%)	29 (66%)	15 (34%)	5 (11%)	1 (2%)
	Flolan	45	1 (2%)	2 (4%)	16 (36%)	29 (64%)	14 (31%)	1 (2%)

Total Subjects with Hemodynamic Data: 48 Conventional, 50 Flolan

More Flolan than conventional therapy patients showed improvement of symptoms using the Borg Dyspnea scale (decreased scores) and using dyspnea-fatigue rating (increased scores). Again not all patients had all assessments done. The sponsor's tables summarizing the symptom data are shown below.

Protocol: VA1A4001
Population: All Subjects, Intent-to-Treat

Table 3
Summary of Borg-Dyspnea Data[1]

Visit	Treatment	Subjects	Subjects with Borg-Dyspnea data	Subjects with a Change in Score < 0	Subjects with a Change in Score = 0	Subjects with a Change in Score > 0
Week 1	Conventional	55	54	15 (28%)	19 (35%)	20 (37%)
	Flolan	56	50	29 (58%)	6 (12%)	15 (30%)
Week 6	Conventional	55	51	17 (33%)	8 (16%)	26 (51%)
	Flolan	52	48	30 (63%)	11 (23%)	7 (15%)
Week 12	Conventional	48	42	12 (29%)	6 (14%)	24 (57%)
	Flolan	51	49	35 (71%)	6 (12%)	8 (16%)

[1]A decrease in the Borg-Dyspnea score (change < 0) indicates improvement.

(1)An increase in the Dyspnea-Fatigue rating (change > 0) indicates improvement.

Population: All Subjects, Intent-to-Treat

Table 4
Summary of Dyspnea-Fatigue Data

Visit	Treatment	Subjects	Subjects with Dyspnea-Fatigue data	Subjects with a Change in Rating < 0	Subjects with a Change in Rating = 0	Subjects with a Change in Rating > 0
Week 1	Conventional	55	55	17 (31%)	34 (62%)	4 (7%)
	Flolan	55	55	10 (18%)	33 (60%)	12 (22%)
Week 6	Conventional	54	54	27 (50%)	20 (37%)	7 (13%)
	Flolan	52	52	7 (13%)	15 (29%)	30 (58%)
Week 12	Conventional	47	47	32 (68%)	10 (21%)	5 (11%)
	Flolan	51	51	8 (16%)	11 (22%)	32 (63%)

No additional information is provided for the endpoints of NYHA functional class, signs and symptoms of scleroderma spectrum of diseases, or survival. Though a smaller number of patients in both treatment groups showed any change in NYHA Class, numerically more Flolan patients than conventional therapy patients showed improvement. Change in Raynaud's severity scores tended to favor Flolan but the difference between the treatment groups was small. Four patients in the Flolan group and 5 patients in the conventional therapy group died during the study. Generally, the Flolan patients died earlier (2-3 weeks) while the conventional therapy patients died at 7-10 weeks.

Reviewer's comments: Regarding efficacy of Flolan in secondary pulmonary hypertension due to scleroderma spectrum of diseases: The sponsors tables show generally good correlation among the results for the various outcome measures for the treatment groups overall. However, these tables do not address how well correlated the results are for the outcome measures within individual patients. Using the patient efficacy data listings provided by the sponsor in this submission I have derived the following table which summarizes relationship between the 6-Minute Walk Test ourtcome and each of the secondary outcomes for each patient at Week-12 evaluation.

Correlation among Outcomes for Primary and Secondary Efficacy Parameters

	12 Week Distance Walked (number of patients)					
	Flolan*			Conventional*		
	Improved* (n=35)	Worse* (n=14)	Missing (n=7)	Improved* (n=12)	Worse* (n=32)	Missing (n=11)
NYHA Class, 12 wks						
Improved	18	3	–	–	–	–
Unchanged	17	11	–	11	22	2
Worse	–	–	2	1	10	2
Missing	–	–	5	–	–	7
Borg Dyspnea, 12 wks						
Improved	28	6	–	6	6	–
Unchanged	5	1	–	1	5	–
Worse	2	6	–	5	19	–
Missing	–	1	7	–	2	11
Dyspnea-Fatigue Rating, 12 wks						
Improved	31	5	–	3	3	–
Unchanged	–	6	1	4	6	–
Worse	4	3	1	5	23	3
Missing	–	–	5	–	–	8
PAPm, 12 wks						
Improved	28	8	1	6	15	1
Unchanged	–	–	–	–	–	–
Worse	7	6	–	6	17	3
Missing	–	–	6	–	–	7
PVR, 12 wks						
Improved	26	13	1	2	15	1
Unchanged	–	–	–	–	–	–
Worse	7	–	–	8	15	3
Missing	2	1	6	2	2	7

* No patients were unchanged with regard to walking distance over the time of the study.
* relative to baseline

reviewer's original table, based on data in sponsor's data listings

Generally, there was a fair amount of within patient correlation among the endpoints with regard to whether or not there was improvement. This was particularly true among the Flolan patients who showed improvement in the 6-Minute Walk Distance at the 12 Week assessment. For these patients, 51%-88% of patients having an increase in walking distance had a concurrent improvement in one or more of the other efficacy endpoints. Among the conventional therapy patients the correlation was less apparent with 0-50% of patients with improved 6 Minute Walking Distance at Week 12 also showing improvement in at least one of the other efficacy parameters. Among the endpoints NYHA Class was least likely to show any change (improvement or worsening) over the course of the study in either of the treatment groups; 50% of Flolan patients and 63% of conventional therapy patients showed no change in NYHA Class at 12 Weeks. It should be noted that this tabulation does not allow comparison of magnitude of effect for the endpoints among individual patients. Though this assessment does not allow an evaluation of how the magnitude of improvement or worsening correlated among the endpoints in this study, it does, however, indicate that at least qualitatively the efficacy endpoints were reasonably well-correlated in this study of secondary hypertension due to scleroderma spectrum of disease.

Interestingly, hemodynamic response in and of itself did not appear to be a particularly good predictor of clinical response to the study drug, particularly for the conventional therapy patients. For instance, among patients who had improvement in both the PAPm and PVR, in the conventional therapy group 1/10 had improved walk distance (12 wks), 8/10 had worse walk distance and 1/10 had missing value for walk; among Flolan

patients with improvement in both PAPm and PVR, 23/32 patients had improved walk distance (12 wks), 8/32 had worse walk distance and 1/32 had missing value for walk. Results for patients who had improvement in both the PAPm and CO were similar. These results are summarized in the following table.

Correlation between Change in Hemodynamic Parameters and Change in 6-Minute Walk Distance at End of Study

	6-Minute Walk Distance at 12 Weeks*		
	Improved	Worse	Missing
Number of Patients with Improvement in Both PAPm and PVR (%)			
Flolan (n=32)	23 (71.9%)	8 (25.0%)	1 (3.1%)
Conventional (n=10)	1 (10.0%)	8 (80.0%)	1 (10.0%)
Number of Patients with Improvement in Both PAPm and CO (%)			
Flolan (n=31)	23 (74.2%)	7 (22.6%)	1 (3.2%)
Conventional (n=7)	1 (14.3%)	6 (85.7%)	0 (0.0%)

* relative to baseline

reviewer's original table, based on data in sponsor's 10/13/99 submission, Attachment 4

The variable relationship between change in hemodynamic parameters and change in clinical symptoms may reflect the complex pathophysiology of pulmonary hypertension as a disease.

There were very few males in the study (4 Flolan; 11 conventional therapy). The males generally did poorly (2/4 males in the Flolan group and 0/11 males in the conventional therapy group showing improvement in 6-Minute Walk distance at 12 Weeks).

Mean age of patients in the Conventional therapy group was 58.2 yrs as compared to 53.0 yrs in the Flolan group. Mean baseline 6-Minute Walk distance in the two groups was the same (about 270 meters). Mean baseline walk among patients who improved on conventional therapy (236 m) was somewhat less than among those who worsened on conventional therapy (288 m); mean baseline walk among patients who improved on Flolan was similar to that in patients who worsened on Flolan (272m and 289m, respectively). Mean age of patients who had improved walking distance at 12 weeks on Flolan was 49.7 yrs as compared to 61.5 yrs for patients who improved on conventional therapy. Mean age of patients who worsened on Flolan was 56.9 yrs as compared to 57.6 yrs for patients who worsened on conventional therapy.

Regarding efficacy of Flolan in secondary pulmonary hypertension due to other causes: The sponsor's 4/28/99 submission (SE1/BM003) included results of a literature search to ascertain the clinical experience with intravenous Flolan use in patients with causes of secondary hypertension other than scleroderma spectrum of diseases (i.e., persistent pulmonary hypertension of the newborn [PPHN], pulmonary hypertension associated with HIV infection, portal hypertension, and congenital causes) identifying 11 studies involving intravenous Flolan treatment protocols [most of which reported no safety information]. The sponsor concluded that the studies "provide little data to support the use of Flolan in these subpopulations" but felt nevertheless, that these did show Flolan to be beneficial therapy in these patients. The 12/22/99 safety update contains 5 additional reports of studies in patients with other causes of secondary pulmonary hypertension. There were no studies of intravenous Flolan treatment of HIV infected patients. The information submitted regarding these other causes of pulmonary hypertension is summarized in the following table. [Note: This summary does not include anectdotal case reports].

Summary of Published Reports of Flolan Use in Secondary Pulmonary Hypertension Due to Causes Other Than Scleroderma Spectrum of Diseases

Reference	Design	Patients	Treatments	Doses and duration	Results	Comments
Persistent Pulmonary Hypertension of the Newborn (PPHN):						
Eronen, M et al (1997)	uncontrolled	8 infants on extracorporeal membrane oxygenation (ECMO)	Flolan	20-120ng/kg/min; median duration of dosing, 3.6 days	sig. decrease in PAP and reversal of ductal shunt	No sig. CNS complications at 2-12 mos but 2 pts had bronchopulmonary dysplasia. 1 pt with muscular hypotonia at 1 yr.
Parker, TA et al (1997)	uncontrolled case report	1 infant with alveolar-capillary dysplasia	Flolan + NO	8ng/kg/min; dose increased up to 230ng/kg/min when pt developed pneumonia; duration of dosing was about 6 wks	initial marked improvement but pt deteriorated over few weeks and died.	Severe systemic flushing with tachycardia at highest dose; infant died of alveolar-capillary dysplasia
Sasse, S et al (1997)	uncontrolled	19 neonates; 7 received IV Flolan	conventional basic therapy followed by norepinephrine, high frequency oscillatory ventilation, IV Flolan and ECMO therapy	dose and duration not given	Flolan reported to be advantageous.	Overall 10% mortality, "no morbidity" related to therapy
Portopulmonary Hypertension:						
Kaisers, U et al (1996)	active control	15 adult patients following liver transplantation	Flolan vs. nitroglycerin	5ng/kg/min x 45 min	Flolan sig superior to nitroglycerin in increasing systemic oxygen delivery, vasodilation, cardiac index and decreasing PAP ($p<0.05$ for all)	No mention of adverse events or safety info for these patients.
Kuo, PC et al (1997)	uncontrolled	4 patients with chronic liver disease	IV Flolan	10-28 ng/kg/min x 6 to 14 months	decreased mean PAP and PVR and increased cardiac output	No mention of adverse events or safety info for these patients.
Plotkin, JS et al (1998)	case report	1 patient with severe portopulmonary hypertension	IV epoprostenol	23ng/kg/min x about 3 months	"supportive of effectiveness"	No mention of adverse events. Epoprostenol stopped at patient's request
Rodriguez, MJ et al (1998)(abs)	uncontrolled	8 patients with portopulmonary hypertension prior to liver transplant	IV epoprostenol	avg dose 10.9ng/kg/min; avg duration about 5 months (range 18-326 days)	sig decrease in PAP and pulmonary artery occlusion pressure	2 patients expired believed due to catheter-related infections
Kuo, PC et al (1996)(abs)	uncontrolled	5 patients with portopulmonary hypertension	IV Flolan	avg. dose 12.2ng/kg/min x 3 to 6 months	decreased mean PAP, PVR and NYHA status and increased cardiac output	no major morbidity related to epoprostenol or delivery system

Krowka, MJ et al (1999)	uncontrolled; case series	15 patients with advanced liver disease and moderate to severe pulmonary hypertension		2-48ng/kg/min; duration of infusion, 8 days-30 months		Dose-limiting side effects in acute phase: systemic hypotension (4), headache (2) and nausea (5). 6/10 pts with long term treatment died most due to advanced liver disease; 1 with sudden death. 1 pt discontinued chronic therapy because of diarrhea; other complaints with long-term treatment included facial flushing, jaw pain, loose bowel movements and lower leg discomfort; one pt developed hepatic deterioration, massive splenomegaly, and progressive thrombocytopenia (65,000 to 6,000 over 18 months of Flolan) and died.
Congenital Causes (systemic to pulmonary shunts):						
Bush, A et al (1987)(review)	dose-respon study	20 children with congenital heart disease (15 prior to surgery; 5 after surgery)	IV Flolan	5-20ng/kg/min duration not given	dose related decrease in PVR; fall in PVR with Flolan additive to that obtained with administration of 100% oxygen	no sig problems; however, mentioned that systemic hypotension may occur and there is a theoretical risk of increased vascular permeability in the lung which would favor pulmonary edema formation in some children and also epoprostenol may stimulate renin release causeing sodium retention and worsening edema.
Bds AP et al (1993)	uncontrolled	52 pediatric patients with diaphragmatic hernia	IV Flolan	5-20ng/kg/min; mean duration not given; 1 pt treated 6 days	sig. decrease in alveolar-arterial oxygen gradient and oxygenation index	No side effects were noted during infusion; 18 of 23 pts with pulmonary hypertension died during the 52 month followup
Schulz-Neick, I et al (abs)(no year given)	uncontrolled	21 patients with congenital heart disease (intracardiac shunting lesions); 5 received Flolan	IV Flolan	15-20ng/kg/min; duration of infustion not given	Reduction of PVR in 16 of 21 patients with oxygen inhalation + IV Flolan; 2 patients discontinued Flolan due to systemic hypotension	In 2 of 5 patients epoprostenol test had to be stopped because of systemic hypotension.
Rosenzweig, EB et al (1999)	uncontrolled	20 patients with congenital heart disease who had failed conventional therapy (including digitalis, diuretics, oxygen, warfarin, calcium channel blockade if indicated and surgery if operable)	IV Flolan	mean dose 82ng/kg/min; mean duration 15 months (range, 8-24 months)	improvement in hemodynamic parameters and exercise tolerance was seen at 1 year followup	Side effects reported acutely and with chronic treatment included jaw pain (14), rash (8), arthralgias (5) and nausea/vomiting (2). dislodged central venous lines (7), local central venous line infections (4) and pump malfunctions (2). "There were no episodes of catheter-related sepsis.".

reviewer's original table based on references in sponsor's 4/28/99 and 12/22/99 submissions

Three other reports of IV Flolan use including patients with connective tissue diseases are included in the 12/22/99 submission.

- Humbert, M et al, Eur. Respir. J. 13:1351 (1999) report an uncontrolled study of 17 patients with pulmonary hypertension and connective tissue diseases (mixed connective tissue disease (MCTD)(3), CREST syndrome(6), systemic lupus erythematosis (SLE)(5), systemic sclerosis (SS)(2) and primary Sjogren's syndrome (1). Patients received Flolan at a dose of 8-28ng/kg/min for 6 wks and were evaluated at 6 weeks then every 3 months. During first 6 weeks 1 MCTD patient died of sepsis and 1 CREST patient died of pulmonary edema. Other patients showed improved clinical and hemodynamic parameters. During followup up to 38 months 5 patients died (right heart failure, 2 (SLE, MCTD); severe sepsis, 2 (MCTD, SLE); syncope and drug delivery system dysfunction, 1(SS)). Seven of the 8 surviving patients continued to have hemodynamic improvement. A number of other adverse events were reported including 15 episodes of catheter-related sepsis in 7 patients [catheter-related sepsis rate was 0.64/yr in this study],5 catheter-related upper limb deep vein thromboses in 3 patients and 5 catheter-related pneumothorax in 5 patients. Other problems included irritation and local infection of the catheter site, jaw pain, flushing, headache, diarrhea, nausea and vomiting.
- McLaughlin, V et al, Ann. Int. Med., 130:740 (1999) describes a case series of 33 patients with severe pulmonary hypertension due to a variety of causes (congenital heart disease, 7; collagen vascular disease, 14; sarcoidosis, 2; peripheral thromboembolic disease, 3; portopulmonary hypertension, 7). Patients were treated with IV Flolan (mean dose 31ng/kg/min; mean duration 12.7 months). Nine patients died during followup: 2 scleroderma, 2 thromboembolic pulmonary hypertension, 3 portopulmonary hypertension, 1 mixed connective tissue disease and 1 congenital heart disease. Common side effects included diarrhea, jaw pain, headaches, and flushing. Seven patients had local catheter site infections and three patients developed sepsis.
- Sanchez, O et al 3rd Congress of Pneumology in the French Language (1999), p. 1S84 (abstract) report that in a series of 57 patients with pulmonary arterial hypertension associated with a collagen disease (scleroderma, 32; systemic lupus erythematosus, 13; mixed collagen disease, 7; Sjogren's syndrome, 3; rheumatoid polyarthritis, 1; polymyositis, 1) only 15/57 (26%) of patients showed and acute vasodilatory response to Flolan or inhaled nitrous oxide. [Number of patients receiving Flolan is not given]. There is no mention of adverse events.

One report comparing NO to epoprostenol for pulmonary hypertension after cardiac operations in 13 children aged 3 days to 12 months epoprostenol was discontinued because of systemic hypotension. All 13 patients studied had a more favorable hemodynamic response to inhaled nitrous oxide than to epoprostenol (Goldman AP et al, 1995).

These publications suggest that epoprostenol may be of benefit in some of these patients and may warrant further study. However, systemic hypotension and sepsis due to long-term vascular access are serious problems with the drug.

Safety Update:
The December 22, 1999 Safety Update covers the period January 1, 1999 through September 15, 1999. During that time there have been no studies completed and no studies initiated. There is one ongoing study, VA1A4002, which is an open-label

extension of Study VA1A4001 and in which patients receive Flolan indefinitely until death, transplantation or marketing approval of Flolan for the indication or until patients elect to discontinue the drug. A total of 97 patients (10 males, 87 females) have received Flolan in this study.

There have been 7 deaths during the reporting period. Causes of death included: right heart failure (2), septic shock (1), gastrointestinal hemorrhage (1), exacerbation of dyspnea (1), sudden death (1) and multiple organ failure (1). Six of the patients were women aged 45-55 years with long history of pulmonary hypertension secondary to scleroderma spectrum of diseases and who had been on Flolan for 14-24 months. The seventh patient was a 60 year old man with pulmonary hypertension secondary to scleroderma spectrum of diseases who was lost-to-followup after two hospitalizations for congestive heart failure and about 5 months on Flolan. The center subsequently found out through a family member that the patient had died of multiorgan failure about 2 months after last being seen at the center. Though none of these deaths were considered related to Flolan, one patient, a 45 year old woman with a history of repeated Hickman catheter placements and line infections died due to sepsis.

This safety update lists 34 non-fatal serious adverse events (occurring in 18 patients), 24 of which occurred prior to January 1, 1999 but were not reported to the sponsor until later. Nonfatal serious adverse events occurring in this study during the reporting period consisted of: renal failure (3 reports), hypotension (3 reports), hypokalemia (2 reports), thrombocytopenia (2 reports), pneumonia/viral pneumonia (2 reports), pneumonthroax (2 reports), bronchitis/acute bronchitis (2 reports) and 1 report each of chest pain, anemia, idiopathic thrombocytopenic purpura, hypovolemia, hyperkalemia, atrial fibrillation, lung nodule(s), air embolism, pericardial effusion [2 reports in 1 patient], thrid degree heart block, syncope, upper respiratory infection, dehydration, cholelithiasis, pleural effusion [2 reports in 1 patient], nausea, flushing, tachycardia diaphoresis, and tension in multiple body sites(s). All these events were considered "unlikely" related to Flolan except for the following which were judged "possible" related to Flolan:

- ITP in a 68 year old female after about 14 months on Flolan;
- thrombocytopenia in a 44 year old woman after about 11 months on Flolan; patient died of exacerbation of right heart failure
- thrombocytopenia in a 66 year old woman after about 25 months on Flolan; patient also had atrial fibrillation, pneumothorax, lung nodule(s); all events resolved with continued Flolan;
- hypotension in a 69 year old woman after 1 month on Flolan 6.66ng/kg/min; the Flolan dose was adjusted;
- nausea, flushing, tachycardia diaphoresis, tension in multiple body sites(s) in a 44 year old woman after about 14 months on Flolan (13ng/kg/min); Flolan dosing was interrupted and symptoms resolved.

The sponsor states that no patients discontinued Flolan prematurely in this study due to an adverse event and there were no pregnancies during the reporting period.

The sponsor reports a total of 383 serious adverse events in 132 cases in domestic spontaneous reports. Events reported in 2 or more patients are tabulated below by body system:

Most Common Serious Adverse Events with Flolan

Event	Number of reports
Blood and Lymphatic	
thrombocytopenia	3
Cardiovascular	
right heart failure	19
progression of primary pulmonary hypertension	18
cardiac arrest	17
exacerbation of right heart failure	12
hypotension	9
pulmonary embolism	7
cardiac failure	6
exacerbation of pulmonary hypertension	6
congestive cardiac failure	4
cardiorespiratory arrest	3
exacerbation of primary pulmonary hypertension	3
pericardial effusion	2
acute myocardial infarction	2
arrhythmia	2
atrial fibrillation	2
bradycardia	2
cerebral hemorrhage	2
cor pulmonale	2
end stage primary pulmonary hypertension	2
progression of secondary pulmonary hypertension	2
pulmonary hypertension	2
secondary pulmonary hypertension	2
septic shock	2
Drug Interaction Overdose and Trauma	
intravascular catheter infection	2
Gastrointestinal	
ascites	4
nausea	4
abdominal pain	2
gastrointestinal hemorrhage	2
Hepatobiliary Tract and Pancreas:	
hepatic failure	2
Lower Respiratory:	
pneumonia	7
respiratory failure	5
shortness of breath	5
exacerbation of dyspnea	4
hypoxemia	4
pleural effusion	3
respiratory arrest	3
adult respiratory distress syndrome	2
dyspnea	2
hemoptysis	2
hypoxia	2
possible aspiration	2
Neurology:	
decreased consciousness	3
disorientation	2
headache	2
loss of consciousness	2
Non-Site Specific:	
multiple organ failure	11
death due to unknown cause	8
sepsis	7
lack of efficacy	6
death	3
exacerbation of underlying condition	3
fever	3
edema	2
infection	2
pallor	2
positive blood culture	2
progression of disease	2
transplant rejection	2
Urology:	
increased creatinine levels	2

reviewer's table, based on sponsor's Table 5, 12/22/99 submission

There have been 7 foreign reports during this time including 2 felt to be "almost certain" related to Flolan. Events included: interstitial pulmonary edema in a woman treated with Flolan for 3 days (U.K.); exacerbation of hypotension [felt possibly related to Flolan], respiratory failure, cardiac failure and death due to progression of disease in a 3 day old infant with congenital diaphragmatic hernia and pulmonary hypertension due to persistent fetal circulation (Japan); hypoxemia, fever, sputum aspiration, bradycardia, cough, increased C-reactive protein and death [felt almost certainly related to Flolan] in a 7 year old girl treated with Flolan for treatment of pulmonary hypertension; oliguria, edema and shock resulting in death 5 days later in a 16 year old girl who received an infusion of Flolan; pancytopenia with WBC 1890 [felt possibly related to Flolan] after about 2 months on Flolan in a 50 year old woman who was also receiving other meds (sulphiride and flomoxef)(Japan); hypotension and pre-shock in a 50 year old woman with NYHA Class III disease started on Flolan for treatment of primary pulmonary hypertension [positive rechallenge; events felt almost certainly related to Flolan]; and exacerbation of right heart failure in a 16 year old girl who had received Flolan on a compassionate-use basis for pulmonary hypertension (Japan); . There has been one pregnancy reported with outcome unknown (U.K.). The two cases felt to be almost certainly related to Flolan are summarized below:

- hypoxemia, fever, increased C-reactive protein levels, bradycardia, cough, aspiration of sputum, and death due to unknown cause in a 7 year old girl with pulmonary hypertension (Japan) - Patient had received multiple medications for pulmonary hypertension. She was started on Flolan at 2ng/kg/min and increased to 10ng/kg/min and developed fever and hypoxemia; Flolan dose was decreased but oxygen saturation did not improve. Patient was give nitrous oxide which improved the oxygen saturation and Flolan was discontinued. Patient developed bradycardia and cough from aspiration of sputum. C-reactive protein was noted. Patient died in spite of supportive therapy.
- decreased blood pressure and shock in a 50 year old woman after receiving Flolan (Japan) – Patient was started on Flolan 2ng/kg/min for treatment of pulmonary hypertension. Dose was gradually increased to 6ng/kg/min and blood pressure dropped to 50mm systolic. Flolan dose was tapered off. Blood pressure returned to normal within 24 hrs. Patient was rechallenged and the events recurred.

The sponsor reports 12 literature references mentioning use of Flolan (165 patients total). Six publications are case reports (11 patients), 5 were treatment protocols (about 74 patients with connective tissue diseases; about 27 patients with hypertension due to congenital causes), and 1 was a prosepective randomized study of Flolan on kidney function during aorto-coronary bypass surgery. All patients received Flolan as part of therapy for pulmonary hypertension. Age range was 1.9-65 years. Flolan dose ranged from 1-48ng/kg/min (not given in 2 reports) and duration of Flolan therapy was 40 minutes to 154 weeks. Adverse events reported were comparable to those already reported for Flolan.

From 9/15/99 to 3/7/00 the FDA has received from the sponsor an additional 55 spontaneous reports (33 initial; 22 followup) of adverse events associated with Flolan exposure. These are tabulated in Appendix A of this review. In 24 of the initial reports, the patient died. In most of these cases reported adverse events reflected consequences of progression of the patient's underlying disease. The events mentioned most frequently in the case reports of patients who died are summarized in the following table.

Initial Spontaneous Reports Submitted from 9/15/99 to 3/7/00: Most Frequently Mentioned Adverse Events in Patients Who Died

Cause of Death	Number of Patients	Report ID Number
cardiac failure/heart failure/ congestive heart failure	9	A0101656A A0102213A A0108203A A0108206A A0109019A A0110138A A0111276A A0112388A A0105635A
hypersplenism/splenomegaly with thrombocytopenia, pancytopenia, leukopenia	3	A0103406A* A0103409A* A0103410A*[a]
thrombocytopenia only		B0077866A
exacerbation of pulmonary hypertension	3	A0102213A A0102313A A0108206A
pulmonary edema	2	A0102822A A0111276A
liver failure	2	A0103410A A0105453A
progression of pulmonary hypertension/lack of efficacy	2	A0111221A A0110694A A0108203A
arrhythmia	2	A0102822A A0099478A

* These 3 cases were in a single literature report
[a] hypersplenism/splenomegaly with thrombocytopenia, leukopenia;

reviewer's original table

There was one case of agranulocytosis reported (A106225A) and one case of glucose intolerance and asymptomatic increased pancreatic enzyme levels (A0111875A) and one case of Interstitial pneumonitis (A0101102A).

Reviewer's comments: Most of the events reported are consistent with the known safety profile of Flolan with symptoms (such as right heart failure, cardiac arrest, dyspnea and progression of pulmonary hypertension) related to the underlying disorder, pulmonary hypertension, predominating followed by problems such as sepsis related to the indwelling intravenous catheter needed for administration of this drug.

However, some events occurring in patients in this updated safety database may not be adequately reflected in the current labeling for Flolan. These include thrombocytopenia (which occurred in 2 Flolan patients in Study VA14001, in 3 patients in the Safety Update and in several patients in the spontaneous reporting database) and pancytopenia (which has been reported in several patients in the spontaneous reporting database); most often these have occurred associated with hypersplenism. There have been 7 reports of pulmonary embolism in the spontaneous reporting database.

The safety evaluation of study VA10001 revealed slightly higher frequency overall of events involving the nervous system, in the conventional therapy group as compared to Flolan; however, "dizziness" was the only nervous system event reported for almost all of the 43 conventional therapy patients having adverse events involving the nervous system. In the Flolan group though 33 of 36 patients reporting events involving the

nervous system experienced dizziness, several patients reported other events involving the nervous system. The nervous system events in Study VA1A4001 are summarized in the following table:

Study VA1A4001: Patients Experiencing Adverse Events Involving the Nervous System

Event	Flolan	Conventional
Nervous system		
Any event	36 (64%)	43 (78%)
dizziness	33 (59%)	42 (76%)
depression	7 (13%)	2 (4%)
anxiety	3 (5%)	2 (4%)
insomnia	5 (9%)	0
somnolence	2 (4%)	1 (2%)
nervousness	2 (4%)	0
paresthesia	2 (4%)	0
confusion	1 (2%)	0
hypesthesia	1 (2%)	0
speech disorder	1 (2%)	0
thinking abnormal	1 (2%)	0
tremor	0	1 (2%)

from sponsor's table, NDA Vol. 30.3 p.154

Neurologic adverse events do not appear prominent in the spontaneous adverse events database.

Labeling:
The sponsor has provided annotated draft labeling (NDA Vol. 36.1, Attachment 2) revised to reflect a change in the requested indication to add "pulmonary hypertension associated with the scleroderma spectrum of disease in NYHA Class III and Class IV patients who do not respond adequately to conventional therapy."

The proposed labeling is acceptable except as follows:

Conclusions and Recommendations:
The sponsor has provided one adequate and well-controlled trial (Study VA1A4001) demonstrating safety and efficacy of Flolan in treatment of pulmonary hypertension secondary to scleroderma spectrum of diseases. Though the statistical significance for the treatment effect in the single study provided for this application is not robust, the result for the scleroderma spectrum of diseases patient population may reasonably be supported by the efficacy results in primary pulmonary hypertension patients. Though a benefit on survival is not demonstrated for these patients with pulmonary hypertension associated with scleroderma spectrum of diseases, the clinical benefits shown appear to be sufficiently meaningful to warrant approval of Flolan for use in this severe, debilitating disease for which treatment options are limited. There is not sufficient efficacy and safety information to allow a recommendation for

I recommend that Flolan be approved for treatment of pulmonary hypertension secondary to scleroderma spectrum of diseases with labeling revisions as indicated under **Labeling** above. Dosing should be initiated at 2ng/kg/min and increased by 1-2ng/kg/min every 15 minutes or longer until dose-limiting pharmacologic effects are obtained or until tolerance to the drug is established.

In addition, I recommend the following:

- The sponsor should provide additional information on Case A0106225A (agranulocytosis in a 34 year old woman with primary pulmonary hypertension).

- The sponsor should examine the safety database for Flolan with regard to neurologic adverse events, particularly for anxiety, nervousness, and depression to see if modifications to the adverse events section of the labeling are warranted.
- The sponsor should examine the epoprostenol safety database for all cases of pneumonitis to see if further modifications to the adverse events section of the labeling are warranted.

/S/

Kathy M. Robie-Suh, M.D., Ph.D. 3/23/00

cc:
NDA 20-444
HFD-180
HFD-180/LTalarico /S/ 3-23-00
HFD-180/KRobie-Suh
HFD-180/BStrongin
HFD-180/JChoudary
HFD-180/LZhou
HFD-720/PFlyer
f/t 3/23/00 jgw

Concur with above comments and recommendation for approval of Flolan for the indication of secondary pulmonary hypertension in patients with scleroderma spectrum of disease —

/S/

3-23-00

APPEARS THIS WAY
ON ORIGINAL

APPENDIX A

Spontaneously Reported Adverse Events (FDA Form 3500A) for Flolan from 9/15/99 through 3/7/00)

Case number[@]	Date submitted	Date Occurred	Description
INITIAL:			
A0101102A	9/23/99	1996	20yo F on Flolan 5 yrs developed **exacerbation of dyspnea, pleural pain, edema, palpitations, tachycardia, dry cough, fatigue, catheter infection; increased 2nd heart sound and acne on face.** Open lung biopsy showed **interstitial pneumonitis**. (publication: Chest 116:569 (1999)
A0101498A	9/27/99	unknown	64 yo F received Flolan for secondary pulmonary hypertension and **died**. No further info.
A0101937A	9/27/99	unknown	17 yo patient with primary pulmonary hypertension on Flolan for 4 yrs developed **gastrointestinal bleed, multiple gastrointestinal ulcers.**
A0102053A*	9/29/99	unknown	adult F with scleroderma (**systemic sclerosis**) received Flolan and died. No other info
A0101656A	9/29/99	unknown	52 year old F with PPH received Flolan and died due to **cardiac failure.**
A0102213A	10/8/99	unknown	60 yo F with end stage PPH on Flolan developed **congestive heart failure, exacerbation of pulmonary hypertension, shortness of breath, ascites.** Pt was hospitalized suffered **cardiac arrest and died.**
B0071498A*	10/12/99	unknown	unidentified pt received Flolan during dialysis developed very severe **bronchospasm** requiring treatment with anesthetics
A0102313A	10/12/99	unknown	51 yo F with PPH on Flolan developed **exacerbation of PPH** and died.
A0102822A	10/12/99	unknown	51 yo M with PPH on Flolan experienced **pulmonary edema** and an **arrhythmia** and died.
B0071876A*	10/15/99	7/24/99	16 yo F with PPH and deteriorating condition started on Flolan developed **vascular pain**, and 4 days later **oliguria** and cardiogenic **shock and died.** causality of shock possibly related to Flolan.
A0103406A	11/1/99	unknown	20yo F with portal vein pulmonary hypertension and cryptogenic cirrhosis developed pancytopenia and hypersplenism 3 months after starting Flolan. Continued on Flolan 18 months later underwent elective splenic embolization and splenectomy; died 2 days later due to uncontrollable hemorrhage. AEs: **hemorrhage, exacerbation of thrombocytopenia; hypersplenism; exacerbation of splenomegaly; infarction of spleen, pancytopenia, leukopenia, inflammation, dyspnea, decreased hemoglobin, decreased bilirubin, hyperalbuminemia.** publication: Liver Transpl. and Surg. 5:362 (1999)
A0103408A	11/1/99	unknown	38yo F with portal vein pulmonary hypertension and cryptogenic cirrhosis received Flolan and developed **hypersplenism, splenomegaly, pancytopenia, leukopenia**, thrombocytopenia, **weight loss.** Hypersplenism felt to be due to Flolan. publication: Liver Transpl. and Surg. 5:362 (1999)
A0103409A	11/1/99	unknown	47 yo F with portal vein pulmonary hypertension, autoimmune hepatitis, cirrhosis, enlarged spleen and mild thrombocytopenia on Flolan about 3 yrs developed hepatic carcinoma with metastases and died. AEs: **liver mass, metastatic liver cancer, heart neoplasm** (metastatic), **hypersplenism, splenomegaly, thrombocytopenia, leukopenia, pancytopenia, right upper quadrant pain, sensation of repletion, decreased hemoglobin.** Liver Transpl. and Surg. 5:362 (1999)
A0103410A	11/1/99	unknown	71 yo F with portal vein pulmonary hypertension, autoimmune hepatitis, palpable spleen, on Flolan 9 months developed **hypersplenism, splenomegaly, thrombocytopenia, leukopenia, exacerbation of liver failure, abnormal biochemistry (), ascites, upper abdominal pain, , decreased hemoglobin.** Pt died due to progressive liver failure. Liver Transpl. and Surg. 5:362 (1999)
A0099478A	11/12/99	8/9/99	56 yo M with PPH on Flolan unspecified length of time developed **arrhythmia** and suffered **sudden death**
A0104579A	11/12/99	unknown	Adult F received Flolan unspecified length of time; developed Graves' disease, toxic goiter, ophthalmopathy. Underwent radioactive iodine treatment.
A0105315A	11/16/99	10/19/99	61 yo F receiving Flolan as continuation of protocol for Flolan in pulmonary hypertension secondary to scleroderma spectrum of diseases; developed mild microcytic anemia and thrombocytopenia, after 9 months on Flolan; several months later had episodes of **hematemesis.** CT showed **gastric and mesenteric varices** and mild **splenomegaly** consistent with **portal hypertension.** Cardiac cirrhosis due to right heart failure considered probable cause of portal hypertension. Pt managed with transfusions, meds. Other AEs: **upper GI hemorrhage, decreased blood pressure, increased pulse rate, decreased hemoglobin, esophageal varices, gastric disease due to portal hypertension.**
A0105453A	11/23/99	11/12/99	64 yo M with secondary pulmonary hypertension (cause not indicated) received Flolan and experienced **dyspnea, lack of efficacy, jaundice, hepatocellular disorder and died.**.
A0108203A	12/29/99	unknown	M with PPH experienced **lack of efficacy** with Flolan; died subsequently due to cardiac failure
A0108206A	12/29/99	unknown	57 yo F with PPH experienced possible **malfunction of drug delivery system** and had **exacerbation of PPH leading to cardiac failure and respiratory failure.** Patient died.
A0108207A	1/10/00	unknown	58 yo F with PPH on Flolan developed **renal disease, unspecified other illness** and died.
A0109019A	1/21/00	unknown	59 yo F with secondary pulmonary hypertension (etiology not specified) received Flolan and died due to **cardiac failure**
A106225A	1/20/99	10/14/99	34 yo F with PPH , common variable immunodeficiency, granulomatous hepatitis, pulmonary

			fibrosis; developed agranulocytosis after 1 yr on Flolan; pt presented with fever, catheter infection; WBC 6,300; dif , no granulocytes; other meds: salbutamol frusemide, warfann, fluoxetine HCl, spironolactone, cephalexin, magnesium salt, potassium salt, normal immunoglobulin, unknown.
B0076053A[3]	2/3/00	1/14/00	12 yo F with PPH on Flolan for 5 months developed atelectasis which resolved over 11 days; then developed tremor of hands which resolved with decreased epoprostenol dose.
A0110138A	2/3/00	1/22/00	40 yo F with PPH received Flolan (unknown duration of treatment) developed cardiac failure and died.
A0111221A	2/14/00	2/6/00	14 yo F with PPH received Flolan (unspecified time) and died due to progression of PPH
A0110694A	1/15/00	unknown	16 yo F with secondary pulmonary hypertension (underlying disease not specified) received Flolan and died; event (progressive secondary pulmonary hypertension)
A0111875A	2/17/00	2/8/00	21 yo F with PPH on Flolan for 1 month developed exacerbation of PPH, nausea, vomiting, glucose intolerance and asymptomatic increased pancreatic enzyme levels
A0111276A	2/18/00	unknown	52 yo M with PPH received Flolan (unknown duration) developed pulmonary edema, congestive heart failure and died due to pulmonary vascular occlusive disease.
A0112388A	2/29/00	unknown	24 yo F with PPH received Flolan (unspecified time), developed an enlarged heart and died due to heart failure
A0105635A	3/7/00	11/9/99	59 yo F with PPH and rheumatoid arthritis; on digoxin and torasemide received Flolan for unspecified time; Flolan was discontinued due to lack of efficacy and pt died 15 hrs later due to "advanced pulmonary hypertension". Death attributed to right heart failure and renal failure.
A0113503A	3/7/00	unknown	50 yo F with secondary pulmonary hypertension received Flolan unspecified length of time; stated that she "did not want to live that way". Flolan was discontinued and pt died the following day.
B0077866A[3]	3/7/00	unknown	19 day old M infant with pulmonary hypertension (unspecified cause); received combination of NO and Flolan, developed thrombocytopenia and died. (pub.: Kingasa, H et al. 6th Meeting of Paediatric Pulmonary Circulation).
FOLLOWUP:			
B0070168A[3]	9/17/99	8/2/99	50 yo F with PPH on Flolan for 2 months developed pancytopenia; had received Flolan 3 wks prior to current course; other meds: flomoxef, sulpiride; ethyl loflazepate, frusemide
A0049909A	9/24/99	3/2/97	46 yo F pt with PPH on Flolan developed rash, shortness of breath and infection which resolved in 3 days. Patient continued on Flolan died 27 months later with right heart failure, respiratory insufficiency congestion of liver, cardiac arrhythmia, progressive PPH. Death attributed to arrhythmia.
A00099592A	9/30/99	unknown	53 yo M with PPH received Flolan and died with excacerbation of PPH and cardiac arrest.. Autopsy showed right heart failure, ascites, pleural effusion, pericardial effusion, hepatosplenomegaly, ascites, congested liver and spleen, worsening primary pulmonary hypertension. Pt med hx included heart failure, pulmonary fibrosis esophageal varices.
A0098410A	10/4/99	8/20/99	11 yo F with PPH hospitalized for transplant work-up, started on Flolan, developed acute pancreatitis, diffuse abdominal pain, anorexia. Events improved on continued Flolan.
A0094426A	10/7/99	11/98	42 yo F with PPH awaiting transplant died after 2 yrs on Flolan. During last 6 months prior to death had progressive dyspnea, exacerbation of right heart failure, progressive edema, chronic renal failure . Days prior to death experienced exacerbation of right heart failure, acute on chronic renal failure, dizziness, hypotension, syncope and fall resulting in head laceration. Developed thrombocytopenia (66,000), hyperkalemia, increased serum creatinine and BUN, exacerbation of dyspnea, weakness, edema, absent pulse and became apneic and died while serum potassium being addressed.
A0099802A	10/12/99	unknown	1yo girl with multiple congenital cardiac disorders received epoprostenol unknown period of time and died. AEs: multiple organ failure, cerebral hemorrhage, cardiac arrest
A0102053A	10/13/99	9/99	72 yo F with pulmonary hypertension, scleroderma (systemic sclerosis), peripheral vascular disease received Flolan for 2 wks developed dyspnea on exertion lower extremity pitting edema, orthopnea and was hospitalized. During hospitalization developed worsened congestive heart failure, sinus tachycardia on ECG, pleural effusion with increased lung markings on X-ray, pulmonary edema, rales, agitation, nausea, vomiting, numbness, tingling, bradycardia, pericardial effusion, elevated CPK-MB levels. On 4th hospital day pt developed agonal respiration, apnea, asystole, became pulseless and died.
B0070168A[3]	10/21/99	8/2/99	[2nd follow-up; see above] 50 yo F with PPH on Flolan for 2 months developed pancytopenia; had received Flolan 3 wks prior to current course; additional other meds: spironolactone, warfarin
B0071876A[3]	10/29/99	7/24/99	16 yo F with PPH received Flolan developed vascular pain, oliguria, shock, decreased blood pressure, increased AST, hyperbilirubinemia, increased LDH levels. Pt died. Fall in blood pressure deemed "almost certainly" related to Flolan.
A0102053A	11/4/99	9/99	[2nd fu report for this pt] 72 yo F with secondary pulmonary hypertension, sclerode3rma, coronary artery disease developed congestive heart failure after 2 weeks on Flolan. Pt died due to congestive heart failure felt related to Flolan.
A0053660A	11/12/99	1996	[2nd FU report for this pt] 58 yo pt with PPH developed hyperthyroidism 6 months after starting Flolan. Underwent thyroidectomy, continued on Flolan (2 yrs). Multiple complaints complications requiring therapy. AEs: hyperthyroidism, coronary artery disorder, occlusion of artery, arterial stenosis, exacerbation of PPH, chest pain, shortness of breath, edema, myalgia(s), decreased appetite, weight loss, weakness, diarrhea, pain in

			legs, gastric irritation, bloating, GI gaseous symptoms, headache, malaise, patchy erythema, cold sensation
A0101498A	11/18/99	unknown	64 yo F receive Flolan unspecified time and died of **hypoxia.**
A0103406A	11/24/99	unknown	20 yo F with portal vein pulmonary hypertension, cryptogenic cirrhosis, splenomegaly received Flolan and developed **pancytopenia, hypersplenism** 3 months later. **Splenomegaly worsened** over next 18 months and **coagulation disorder** developed. Pt died due to massive **hemorrhage** after undergoing splenectomy. Other AEs: **sepsis, exacerbation of thrombocytopenia, liver disease decompensation, infarction of spleen, leukopenia, inflammation, dyspnea, decreased hemoglobin, decreased bilirubin**
A0090812A	11/23/99	4/14/99	68 yo F pulmonary hypertension secondary to scleroderma spectrum of diseases; hx **thalassemia minor, breast cancer, atrial fibrillation**; received Flolan about 13 months, developed **decreased platelet levels, fever, ascites, epistaxis, intravascular**; dx **idiopathic thrombocytopenic purpura**; also had **catheter infection, increased white cells**; months later suffered **gastrointestinal bleed, loss of consciousness, respiratory acidosis** and died.
A0103408A	11/23/99	unknown	(see initial report above); followup report does not appear to have any new info
A0103409A	11/23/99	unknown	(see initial report above) pt died due to liver failure secondary to the tumor; not related to splenomegaly
A0103410A	11/23/99	unknown	(see initial report above); pt died due to liver failure related to the underlying disease and not related to splenomegaly
A0100547A	12/22/99	8/4/99	36 yo F with sarcoidosis and pulmonary hypertension received Flolan developed **intravascular catheter infection** and died due to **sepsis**
B0073915A	12/23/99	5/15/99	26 yo F with PPH received Flolan. On day 3 of treatment experienced **decreased cardiac output** which improved with continued Flolan over about 2 weeks. event considered possibly related to Flolan.
B0070168A[a]	12/28/99	8/2/99	[3rd followup; see above] 50 yo F with PPH developed **pancytopenia** and **septic shock** after treatment with Flolan for 2 months. Pt on other meds as well. Not clear if event due to Flolan
B0073915A[a]	1/6/00	5/15/99	[2nd followup; see above] pt with **decreased cardiac output** on Flolan; concurrent meds.: frusemide, warfarin, spironolactone, digoxin, oxygen
A0110694A	1/17/00	unknown	16 yo F with secondary pulmonary hypertension (underlying disease not specified) received Flolan and died; event (**progressive secondary pulmonary hypertension**) judged not related to Flolan

[a]Case number from FDA Form 3500A;
PPH= primary pulmonary hypertension; F=female; M=male; yo= years old; FU=followup
a =Japan; b=foreign other than Japan

Bold type indicates listed adverse events.

* also see followup report

reviewer's original table

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA:	20-444 MAY 26 1999
Document Identification:	SE1-003; C (Safety Update); SE1-003BZ; SE1-003BZ
Sponsor:	GlaxoWellcome
Drug name:	FLOLAN (epoprostenol sodium) for Injection
Indication:	Treatment of secondary pulmonary hypertension
Date submitted:	December 11, 1999; April 20, 1999; April 23, 1999; May 6, 1999
Date Received:	December 14, 1999
Review completed:	May 25, 1999
Reviewer:	Kathy M. Robie-Suh, M.D., Ph.D.

Background and Rationale:
FLOLAN is the synthetic sodium salt of epoprostenol (prostacyclin, PGI2, PGX). Epoprostenol is a prostaglandin derived from arachidonic acid produced mainly in the vascular endothelium by microsomal enzymes. It is a potent vasodilator and inhibitor of platelet aggregation. FLOLAN is indicated "for the long-term intravenous treatment of primary pulmonary hypertension in NYHA Class III and Class IV patients." (Approval date 12/20/95). As of July 1998 FLOLAN has been approved in 4 countries (Canada, France, Israel and U.S.A.) for use in primary pulmonary hypertension (PPH)) and in 11 countries including Austria, Belgium, Denmark, Ireland, Italy, Luxembourg, Netherlands, New Zealand, Singapore, Spain, and United Kingdom) for use in hemodialysis. Current labeling for FLOLAN is attached to this review as Appendix A.

In this application the sponsor seeks approval of FLOLAN "for the long-term treatment of pulmonary hypertension due to [redacted] in NYHA Class III and Class IV patients who do not respond adequately to conventional therapy."

Material submitted:
The submission consists of 24 volumes with pertinent contents as follows:

- Vol 4.001 - Application summary; draft labeling; reviewer's guide
- Vols 4.002 through 4.014 - Clinical section
- Vol 4.015 - Statistical section
- Vol 4.016 - Case report tabulations
- Vol 4.017 through 4.024 - Case report forms

For this review information in all 24 volumes was examined.

Overview of Studies Done with FLOLAN:
FLOLAN has been studied in small numbers of patients for a variety of indications. The sponsor's table of all clinical studies done with FLOLAN is attached to this review as Appendix B. The table below summarizes numbers of patients exposed to FLOLAN in each of the different study populations.

Summary of Numbers of Patients in FLOLAN Studies

Indication	Number of Controlled Studies/ Uncontrolled Studies & Publications only	Number of Patients Exposed to FLOLAN (studies/uncontrolled & publications only[a])
Secondary pulmonary hypertension	1/5	56/132
Primary pulmonary hypertension	2/	106/74
Congenital heart disease	--/21	--/21
Hemodialysis	--/1[b]	--/5
Hepatic failure	--/1	--/1
Pulmonary veno-occlusive disease	--/1	--/1
Persistent pulmonary hypertension of the newborn	--/1	--/1
Raynaud's phenomenon	--/1[b]	--/12
Refractory heart failure	--/1[c]	--/8
Sepsis	--/1	--/16

[a] some patients may have been counted twice
[b] cross-over study
[c] parallel groups, active control

reviewer's original table

Clinical Studies for Efficacy:
The sponsor has investigated the effectiveness of FLOLAN in secondary pulmonary hypertension due to the scleroderma spectrum of diseases (SSD). SSD includes patients with systemic sclerosis, CREST syndrome (calcinosis cutis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangectasia), and the overlap syndrome/mixed connective tissue disease (MCTD). SSD also includes patients who may have one or more features of the individual diseases but who also have accompanying Raynaud's and a positive antinuclear antibody test or nailfold capillary changes. Patients with SSD develop fibrotic changes in the connective tissue and may have vascular abnormalities as well and these effects in the lung result in pulmonary hypertension. It is estimated that about 33% of patients with systemic sclerosis and 50% of those with the CREST syndrome have pulmonary hypertension. The sponsor estimates that Current therapy for pulmonary hypertension due to SSD is limited. Some patients have been reported to respond to captopril, nifedipine and prazosin; however, the long term response to these drugs has not been reliable.

This application contains two clinical trials of FLOLAN in secondary pulmonary hypertension. One study (Study VA1A4001) is a multicenter, randomized, open-label trial of FLOLAN versus standard therapy for 12 weeks in 111 patients with pulmonary hypertension secondary to SSD. The other study (Study VA1A4002) is an open-label extension of Study VA1A4001 where 97 patients have received FLOLAN for up to 64 weeks for treatment of secondary pulmonary hypertension. The sponsor also refers to two controlled clinical trials in primary pulmonary hypertension used to support the approval of FLOLAN for that indication and to other supporting information in secondary pulmonary

hypertension and a variety of other diseases including congenital heart disease, hemodialysis, hepatic failure, pulmonary veno-occlusive disease, persistent pulmonary hypertension of the newborn, Raynaud's phenomenon, refractory heart failure and sepsis.

Studies VA1A4001 and VA1A4002 are summarized and discussed below.

Summary of Pivotal Efficacy Trial:
Title: Protocol VA1A001: A Multicenter, Open-Label, Randomized, Parallel Comparison of the Safety and Efficacy of Chronic FLOLAN (epoprostenol sodium) Infusions Plus Conventional Therapy to Conventional Therapy Alone in Patients with Pulmonary Hypertension Secondary to the Scleroderma Spectrum of Diseases: A Twelve-Week Study (NDA Vols. 4.003 through 4.007; study protocol in Vol. 4.005, pp. 5 through 72).

A. **Objectives:** Primary aims: To evaluate the effect of continuous FLOLAN infusions plus conventional therapy on exercise capacity compared to conventional therapy alone, and to evaluate the safety of continuous infusions of FLOLAN plus conventional therapy compared to conventional therapy alone.

Secondary objectives included evaluation of FLOLAN plus conventional therapy compared to conventional therapy alone on cardiopulmonary hemodynamic parameters, clinical signs and symptoms of pulmonary hypertension, and clinical signs and symptoms of the scleroderma spectrum of diseases, and survival.

B. **Study design:** This was a multicenter, randomized, open-label, parallel group trial of FLOLAN plus conventional therapy versus conventional therapy alone for 12 weeks in patients having pulmonary hypertension due to scleroderma spectrum of diseases. Treatment assignment was to be stratified by vasodilator use and Baseline (yes/no) and exercise capacity at Baseline (50 to <200meters/ ≥ 200meters) and randomization was to be blocked (block size = 4).

NOTE: IN THE TABLES AND DISCUSSIONS IN THIS REVIEW THE CONVENTIONAL THERAPY GROUP IS REFERRED TO AS "CONVENTIONAL GROUP" AND THE CONVENTIONAL THERAPY PLUS FLOLAN GROUP IS REFERRED TO AS THE "FLOLAN GROUP".

C. **Subjects:** These were to be 100 male or female patients aged ≥ 16 years having moderate to severe pulmonary hypertension secondary to the scleroderma spectrum of diseases. In addition, females of child-bearing potential must have a negative pregnancy test at baseline and use an acceptable contraception during the study and females must be non-lactating. Patients must:

- provide written informed consent;
- be capable of (or have a caretaker capable of) reconstituting FLOLAN, operating the infusion pump, and maintaining the central venous catheter;
- be able to walk at least 50 meters in 6 minutes in the baseline exercise test;
- have moderate to severe pulmonary hypertension based on a cardiac catheterization performed at baseline (i.e. mean pulmonary artery pressure (PAPm) ≥ 35mm Hg and pulmonary capillary wedge pressure (PCWP) or left ventricular end diastolic pressure (LVEDP) ≤ 15mm Hg and pulmonary vascular resistance (PVR) ≥ 3mm hg/L/min and right atrial pressure (RAP) ≤ 20mm Hg and absence of congenital heart disease (except patent foramen ovale is ok));
- have a ventilation perfusion scan or pulmonary angiography not indicative of thromboembolic disease, performed since the diagnosis of pulmonary hypertension;

- have pulmonary function tests, performed within the last 3 months, showing total lung capacity (TLC) at least 70% of predicted, or if TLC is 60-70% of predicted, then high resolution CT within the last 3 months must show no more than mild interstitial lung disease, and:
- if on corticosteroid therapy, patient must be treated with a stable dose of prednisone $\leq$10mg/day (or equivalent dose of another steroid) for at least one month prior to entry.

Exclusion criteria: Patients must not have any of the following:

- new chronic therapy for pulmonary hypertension or scleroderma spectrum of diseases added within the last month, except anticoagulants;
- medication used to treat pulmonary hypertension or scleroderma spectrum of diseases discontinued within the last week, except anticoagulants;
- current treatment with any type of prostaglandin therapy;
- any disease other than scleroderma spectrum of diseases known to cause pulmonary hypertension;
- any serious illness that may in the judgement of in the investigator preclude entry into the study (e.g., significant renal dysfunction as evidenced by serum creatinine >2.5mg/dL);
- contraindication to anticoagulation other than elevated prothrombin time (PT) at Baseline due to right heart failure with liver congestion;
- any physical condition which would contraindicate the use of FLOLAN;
- participation in any study of an investigational drug within the past 30 days;
- current or past history of documented recurrent episodes of thrombosis/embolism that would, in the judgement of the investigator, increase the risk of catheter-related thrombosis.
  [Reviewer's note: This last exclusion criterion was added 9 months into the study].

For this study scleroderma spectrum of diseases includes the following:

1. Systemic sclerosis (scleroderma) – characterized by proximal scloeroderma (scleroderma proximal to the metacarpophalangeal joints of the hand), or two of the following:
   - sclerodactyly
   - digital pitting scars or loss of substance of the finger pad
   - bibasilar pulmonary fibrosis radiographically.

2. Limited scleroderma (the CREST syndrome) – defined as having 3 of the following:
   - Subcutaneous calcification
   - Raynaud's phenomenon
   - esophageal dysfunction (defined clinically)
   - sclerodactyly
   - telangiectasia

3. Overlap syndrome – defined as having features of sclerderma and another connective tissue disease including 1 of the 3 following:
   - MCTD or
   - polymyositis or
   - polyarthritis

D. Study drug: Patients were randomized to receive either: (1) conventional therapy alone, or (2) conventional therapy plus FLOLAN by continuous infusion. FLOLAN was provided as a sterile freeze dried powder in glass vials. FLOLAN powder was reconstituted with sterile glycine buffer diluent supplied in 50mL glass vials containing 94mg glycine, 73.5mg sodium chloride, sodium hydroxide (to adjust pH) and Water for Injection.

Composition of FLOLAN Powder

Ingredient	Amount per vial
epoprostenol	0.5 or 1.5mg
glycine	3.76mg
sodium chloride	2.93mg
mannitol	50mg
sodium hydroxide	to adjust pH*

* reconstituted FLOLAN has a pH of 10.2 to 10.8 and is increasingly unstable at lower pH.

FLOLAN was administered via central venous catheter using an ambulatory infusion pump. (Temporary use of peripheral access was allowed until central venous access could be established).

Infusion was to be initiated at 2ng/kg/min and increased by 1-2ng/kg/min every 15 min or longer until dose-limiting pharmacologic effects were obtained or until tolerance to the drug was established. (The most common dose-limiting effects in the PPH controlled clinical trials were nausea, vomiting, headache, hypotension, and flushing). Mean maximum tolerated infusion rate in the PPH trials was 8.6 ± 0.3ng/kg/min. If a patient is not able to tolerate the starting dose of 2ng/kg/min, a lower dose was tried.

Dosing of FLOLAN was based on clinical signs and symptoms such as persistence, recurrence, or worsening of the patient's symptoms of pulmonary hypertension and occurrence of adverse events.

Only doses of FLOLAN that were maintained for at least 12 hours were recorded in the patient's case report form.

Because the FLOLAN patients had an indwelling central venous catheter, all patients in both treatment groups were to receive (in addition to randomized medication) anticoagulant therapy sufficient to maintain the PT ratio at an INR ≥ 1.5 but < 2.0 unless deemed medically necessary by the investigator. (However, there were no provisions for PT to be recorded in the patient case report forms). Patients having a history of thrombosis/embolism and either a positive anti-cardiolipin (ACL) antibody or elevated partial thromboplastin time (PTT) were to have PT maintained at INR of 2.0-2.5.

E. Study plan: The sponsor's table showing schedule of study procedures is shown below:

Overall Time and Events Schedule

Event	Screen	Baseline (-5 days)	Treatment		
			Week 1 (±2 days)	Week 6 (±5 days)	Week 12 (±7 days)
Informed consent	X				
Inclusion/exclusion criteria	X				
Demographics	X				
Medical history	X				
Exercise capacity test	X[a]	X[b]	X	X	X
Borg-Dyspnea scale	X[a]	X[b]	X	X	X
Dyspnea-Fatigue rating		X	X	X	X
NYHA Class		X	X	X	X
Hemodynamic parameters		X			X[c]
Digital ulcer count		X		X	X
Hematology Clinical Chemistry[c]		X			X
Pregnancy test		X			
Randomization		X			
Concomitant medications	X	X----------X----------X----------X			
Adverse experiences		X----------X----------X----------X			
Disease-related events		X----------X----------X----------X			
Raynaud's severity diary		X----------X----------X----------X			

[a] The Screening 6-minute walk (a practice test) may be given up to 6 weeks prior to Baseline.
[b] The Baseline 6-minute walk must be administered at least 1 day after the Screen 6-minute walk.
[c] Lab assessments included hemoglobin, quantitative platelet count, WBC count, serum creatinine, BUN, alkaline phosphatase, and ALT [SGPT]; in addition, patients with history of documented recurrent episodes of thrombosis/embolism were to have an ACL antibody and PTT done at screening to rule out antiphospholipid syndrome.

sponsor's table, NDA Vol. 4.005, p. 48

Potential subjects were screened with determination of exercise capacity, cardiopulmonary hemodynamic parameters, clinical laboratory tests, clinical signs and symptoms of pulmonary hypertension, Raynaud's severity and presence of digital ulcers. Informed consent was obtained. Qualified patients were randomized to one of the two study treatments, with randomization being stratified by center, vasodilator use at Baseline, and exercise capacity at Baseline. Study treatment for patients randomized to conventional therapy was to start immediately after randomization while therapy for the FLOLAN group, conventional therapy was to start immediately with FLOLAN being initiated within 24 hrs of randomization.

Exercise capacity was assessed by the 6-minute walk test. This was to be carried out in a premeasured area 20-30 meters (65-96 feet) long and at least 4 to 8 feet wide. The distance was to be marked off in 5 foot intervals. The area was to be well-ventilated and at a temperature of 68°-76°F. During walk testing all patients were to wear an ambulatory pump and a loose fitting hospital gown over their clothes to mask the presence of absence of a chronic indwelling catheter. Patients were allowed to stop in place and rest as needed during the test. Total distance walked in 6 minutes was recorded. Sites were to try to have the same tester for each patient throughout the study. At Baseline, Week 1, Week 6, and Week 12 all patients were to have Dyspnea-Fatigue Rating (See Appendix D) and NYHA Class assessment (See Appendix E) done immediately prior to starting the 6 Minute Walk Test. On these same days immediately upon completion of the walk test the

patient's dyspnea was to be assessed using the Borg Dyspnea Scale (See Appendix C). Digital ulcers were noted and quantitated at Baseline Week 6 and Week 12. Raynaud's severity was assessed weekly.

Cardiopulmonary hemodynamic parameters were assessed assessed using ——— catheterization. Measurements included systemic arterial O_2 saturation , pulmonary arterial O_2 saturation, mean pulmonary arterial pressure, mean right atrial pressure, mean systemic arterial pressure, pulmonary capillary wedge pressure, heart rate, cardiac output, and calculated measurements of cardiac index and pulmonary vascular resistance.

All patient deaths occurring at any time were to be recorded in the case report form with details of circumstances.

F. **Efficacy parameters:** The primary efficacy parameter specified in the protocol was exercise capacity as measured by the maximum distance walked in meters during the 6-minute walk test after 12 weeks of study drug treatment.

Secondary efficacy parameters included:

- the 6-minute walk results at Week 1 and Week 6,
- cardiopulmonary hemodynamic parameters (mean change from baseline),
- clinical signs and symptoms of pulmonary hypertension as assessed using the Borg Scale, the Dyspnea-Fatigue Rating, and NYHA functional class.
- clinical signs and symptoms of the scleroderma spectrum of diseases as assessed using digital ulcer counts and Raynaud's severity score
- survival over 12 weeks

G. **Statistical methods:** The sponsor estimated that the sample size of 50 patients per treatment group would provide 80% power to detect a difference of 50 meters in the average change from baseline for the 6-minute walk test at the 0.05 level using a 2-tailed test.

Primary analysis of the primary efficacy variable (6-minute walk test after 12 weeks) was to be done: "using nonparametric covariance analysis principles within the randomization framework of the extended Mantel-Haenszel test. Specifically, a Cochran-Mantel-Haenszel correlation statistic will be used on the residuals from an ordinary least squares regression of the ranks of the distance walked". Patients who were missing data because of being too ill to walk were assigned lowest rank. Baseline walk and vasodilator use at baseline were included as covariates. A secondary parametric analysis of covariance also was performed. For the parametric analysis last observation was to be carried forward.

Other secondary analyses included nonparametric analysis of the Week 1 and Week 6 walk data.

Secondary analyses include parametric analysis of the primary efficacy variable and analysis of the 6-minute walk test after 1 and 6 weeks.

Patients unable to walk due to their disease or death were assigned the lowest rank. Baseline walk and vasodilator use at Baseline were included as covariates in the linear regression analysis.

Survival over 12 weeks was to be compared between treatment groups using a log rank test.

Adverse events were to be tabulated and displayed by body system and the incidence of events in the two groups was to be compared. There was no specific method for this comparison specified in the protocol. For of the clinical laboratory data "clinically significant changes" from baseline were to be tabulated.

H. **Safety assessment:** All adverse events occurring during the study were to be recorded in the case report form including assessment as to seriousness, severity, onset and resolution, action taken and investigators' impression of relatedness to study medication.

Special forms were supplied for listing two particular kinds of experiences as follows:

- Disease-Related Events (certain conditions of the disease under study) – These were listed as follows:
  - -- events possibly attributable to pulmonary hypertension: anorexia, ascites, cardiovascular collapse, chest pain, cool extremities, cough, cyanosis, diaphoresis, dizziness, dyspnea on exertion, edema, exercise intolerance, fatigue, hypoxia, loss of consciousness, orthopnea, pallor, palpitations, shortness of breath at rest, syncope, tachycardia, and weight loss.
  - -- events possibly attributable to scleroderma spectrum of diseases: arthralgias, arthritis, calcinosis, digital ulcers, esophageal dysfunction (dysphagia), Raynaud's phenomenon, sclerodactyly, and telangiectasia. Patients were queried at each visit for occurrence of these specific events.

- Events Associated with the Drug Delivery System – These included events associated with the infusion pump, the peripheral tubing and cassettes, and the indwelling central catheter. Adverse events were to be recorded along with information about the associated malfunction. Examples of these events were given in the protocol but not on the CRF and included:
  - -- pump malfunctions (such as battery failure, erased pump memory, improperly attached cassette, interrupted delivery, pump not turned on, uncontrolled delivery ("runaway"), and use of improper battery)
  - -- catheter complications (such as air emboli, bacteremia, catheter clots, catheter colonization, catheter emboli, catheter occlusion, cellulitis, dermatitis, fungemia, pain at catheter site, sepsis, and thrombosis.

Clinical laboratory studies were obtained at Baseline and at Week 12.

I. **Amendments:** There were three amendments to the study protocol. The first two were made prior to any patient enrollment. The third one was made about nine months into the study. [Note: In the submitted materials the sponsor appears to

have used the same cover sheet for all three amendments forgetting to change the date for the later two amendments].

1. Amendment 1: date, 9/23/96 – This amendment clarified some of the entry criteria for the study, the randomization process for the study, the procedure for initiating the FLOLAN infusion, and added a second statistical method (a parametric analysis of covariance) for evaluating the primary endpoint of exercise capacity.

2. Amendment 2: date, 10/7/96 – This amendment further clarified and refined entry criteria and changed method of scoring Raynaud's severity to ordinal scale (integers 1 to 10).

3. Amendment 3: date 7/28/97 -- This amendment was instituted several months after enrollment of patients had begun. It provided for the participation of Canadian-based sites and revised exclusion criterion #9 from:

> "(Patients must not) have a current or past medical history of a venous thrombembolic event (or if having such an event, patients must not have a positive lupus anticoagulant test obtained since screening)."

to:

> "(Patients must not) have a current or past medical history of documented recurrent episodes of thrombosis/embolism that would, in the judgement of the Investigator, increase the risk of catheter-related thrombosis."

The sponsor states that this change was made to exclude patients who may be hypercoagulable due to antiphospholipid antibody syndrome (APS) and therefore at increase risk of thromboembolism from the indwelling catheter required for FLOLAN therapy. The protocol was further modified to indicate that patients with suspected or confirmed APS should receive additional anticoagulation to reduce the risk of developing a thromboembolic event from the indwelling catheter used with FLOLAN therapy. (Maintain PT ratio at INR 1.5-2.0; if patient has current or history of recurrent thrombosis/embolism and either a positive anticardiolipin (ACL) antibody or elevated partial thromboplastin time (PTT), the INR should be maintained at 2.0-2.5). All patients in both treatment groups were to be on anticoagulation for the entire 12-week study period unless some contraindication arose.

J. Results:

A. **Investigators:** This study was carried out from 10/24/96 through 2/26/98 at 16 clinical sites in the U.S. and one in Canada. Investigators and number of patients enrolled at each site are summarized in the following table:

Enrollment of Patients by Study Center/Investigator

Site	Investigator	Number of patients			
		Patients Screened but not Randomized	Patients Enrolled		
			Total Patients	FLOLAN	Conventional Therapy
01	Robyn J. Barst, M.D. Columbia-Presbyterian Medical Center Pediatric Cardiology Center New York, NY	0	7	3	4
02	Lewis J. Rubin Univ. of Maryland School of Medicine Div. of Pulmonary & Critical Care Baltimore, MD	2	7	2	5
03	Stuart Rich, M.D. Rush Heart Institute Section of Cardiology Chicago, IL	8	13	8	5
06	Victor Tapson, M.D. Duke University Medical Center Division of Pulmonary Medicine Durham, NC	2	11	6	5
07	David Badesch, M.D. Univ. of Colorado Health Sciences Center Division of Pulmonary Denver, CO	4	9	4	5
08	Robert Bourge, M.D. Univ. of Alabama at Birmingham Div. of Cardiovascular Diseases School of Medicine Birmingham, AL	0	4	3	1
09	Bruce Brundage, M.D. Harbor-UCLA Medical Center Div. of Cardiology Torrance, CA	22	8	6	2
10	Nicholas S. Hill, M.D. Rhode Island Hospital Pulmonary Division Providence, RI	2	3	1	2
11	Srinivas Murali, M.D. Univ. of Pittsburgh Medical Center Transplant Cardiology Pittsburgh, PA	2	8	2	6
12	David Ralph, M.D. University of Washington Division of Pulmonary & Critical Care Medicine Seattle, WA	0	4	1	3
13	Michael McGoon, M.D. Mayo Clinic Cardiovascular Diseases and Internal Medicine Rochester MN	1	10	7	3
14	David Langeleben, M.D. Jewish General Hospital Cardiology Department Montreal Quebec, Canada	5	2	2	0
15	Adaeze Frost, M.D. Baylor College of Medicine Pulmonary Section Houston, TX	2	6	3	3
17	James E. Loyd, M.D. Vanderbilt University Division of Allergy, Pulmonary, and Critical Care Medicine Nashville, TN	21	10	5	5

22	C. Gregory Elliott, M.D. LDS Hospital Pulmonary Division Salt Lake City, UT	1	3	1	2
23	Reda E. Girgis, M.D. Wayne State University Division of Pulmonary and Critical Care Detroit, MI	0	5	2	3
25	Robert Schilz, D. O. Cleveland Clinic Foundation Dept. of Pulmonary and Critical Care Cleveland, OH	0	1	0	1

from sponsor's table, NDA Vol. 30.3, pp. 95 and 96 and NDA Vol. 33.1, submission dated 5/6/99, pp. 6 through 8

[ ]

B. **Disposition of Patients:** Of 189 patients screened for this study, 111 were enrolled and received study treatment with study regimen. A few patients had some violation of the entry criteria. Four FLOLAN and 3 conventional treatment patients had one hemodynamic parameter slightly outside the range specified in the study inclusion criteria. One FLOLAN patient had pulmonary function testing done outside the 3-month window required for study entry and one conventional treatment patient had a past history of deep venous thrombosis.

Five patients were assigned to the wrong stratum. These included 2 FLOLAN patients assigned to the '≥200meters walking distance' stratum who had baseline walks of 187.5 and 192 meters and one conventional therapy patient who walked 200meters at baseline but was placed in the '<200 meters' stratum. Two FLOLAN patients randomized to the 'no vasodilator' stratum were using a vasodilator at baseline.

The disposition of the 111 enrolled patients is summarized in the following table:

Study VA1A4001: Disposition of Patients

	Number of Patients		
	All Patients	Conventional	FLOLAN
Patients screened	189		
Patients randomized	117		
Patients who received any study drug	111	55	56
Patients who received any study drug and who discontinued study prematurely due to:			
Adverse event	0	0	0
Consent withdrawn	2	1[a]	1[c]
Lost-to-follow-up	1	1[b]	0
Patients who completed study	108	53	55
Deaths	9	5	4
Reason for premature drug discontinuation:	—	—	
Adverse event			2[d]
Death			2[e]
Transplantation			0
Consent withdrawn			1
Lost-to-follow-up			0
Protocol violation			0

[a] Pt #06301, a 34 year old woman with overlap syndrome, withdrew consent for study participation sometime after 6 weeks for unclear reasons. She had suffered 2 serious event during the study (hypoxia and exercise intolerance).

[b] Pt #03307, a 43 year old woman with overlap syndrome, was lost-to-follow-up after the 6 week visit.

[c] Pt #07307, a 56 year old woman with limited scleroderma, withdrew consent after the week 1 visit because of chest pain.

[d] Pt #09302, a 39 year old woman with systemic sclerosis, suffered pulmonary edema 9 days after being randomized. FLOLAN was discontinued but patient died 17 days later with septic shock. Pt #8303, a 67 year old man with limited scleroderma, had FLOLAN discontinued after the week 1 evaluation because of a fatal myocardial infarction.

reviewer's table, based on sponsor's table, NDA Vol. 30.3, p. 102

Five conventional therapy patients and 4 FLOLAN patients died during the study. These patients are discussed under the Safety section below. In the conventional therapy group 2 deaths were due to respiratory failure, 1 to progressive right heart failure, 1 to pulmonary edema and 1 to arrhythmia. In the FLOLAN group 1 patient died of septic shock, 1 patient died of myocardial infarction, 1 had progressive right heart failure and 1 suffered sudden death.

C. Demographics and Baseline Characteristics: Demographic features and baseline characteristics of the patients randomized who received study drug are summarized in the following table:

Study VA1A4001: Demographic Features of the Study Population

Feature	Conventional (n=55)	FLOLAN (n=56)
Age (yrs)		
mean	57.3	53.0
median	59.3	52.6
range	32-78	23-77
Sex		
male	10 (18%)	5 (9%)
female	45 (82%)	51 (91%)
Race		
White	44	49
Black	5	3
Oriental	0	1
Other	6	3
Height (cm)		
mean	165	163
median	164	165
range	145-187	145-179
Weight (kg)		
mean	74.7	70.2
median	73.0	68.1
range	39-119	42-127
Actual weight/ideal weight		
lower than 20%	1 (2%)	1 (2%)
within 20%	22 (40%)	27 (48%)
greater than 20%	32 (58%)	28 (50%)

reviewer's table, from sponsor's tables, NDA Vol. 30.3, pp 104 and 105

There were slight imbalances in a number of demographic factors; however, none of these reached statistical significance. There was a strong trend toward older age in the conventional group as compared to the FLOLAN group (p=0.055); there were twice as many men in the conventional group as in the FLOLAN group (18% vs 9%), there were patients with history of smoking in the conventional group (50% vs. 36%), and there was a greater percentage of patients more than 20% over ideal body weight in the conventional group (58% vs. 50%).

The following table summarizes a number of characteristics of the patient population with regard to the scleroderma spectrum of diseases and risk factors for exacerbation of disease activity or symptomatology.

Study VA1A4001: Baseline Characteristics and Risk Factors of the Study Population

	Conventional (N=55)	FLOLAN (N=56)
NYHA Class		
II	4 (7%)	1 (2%)
III	45 (82%)	42 (75%)
IV	6 (11%)	13 (23%)
Vasodilator use		
no	17 (31%)	18 (32%)
yes	38 (69%)	38 (68%)
Walk category		
<200 meters	11 (20%)	16 (29%)
>200 meters	44 (80%)	40 (71%)
Dyspnea-Fatigue Rating at Baseline		
mean	4.1	3.4
median	4.0	3.0
range		
Borg Dyspnea Score at Baseline		
mean	5.1	5.8
median	5.0	5.0
range		
Raynaud's Severity Score at Baseline		
mean	4.5	4.7
median	4.0	4.0
range		
Scleroderma Spectrum of Disease (SSD) diagnosis		
limited scleroderma	39 (71%)	38 (68%)
overlap syndrome	6 (11%)	8 (14%)
features of SSD	3 (5%)	3 (5%)
systemic sclerosis	7 (13%)	7 (13%)
Duration of pulmonary hypertension history (mos)		
mean	15.2	14.5
median	8	8
range		
Duration of scleroderma history (mos)		
mean	94.8	85.9
median	57	60
range		
Smoking		
past history	25 (45%)	19 (34%)
present at screening	3 ((5%)	1 (2%)
no	27 (49%)	36 (64%)
Use of anorexic agents		
past history	6 (11%)	8 (14%)
present at screening	0	0
no	49 (89%)	48 (86%)
Residence at high altitude		
past history	5 (9%)	3 (5%)
present at screening	1 (2%)	0
no	49 (89%)	52 (93%)
unknown	0	1 (2%)
Deep vein thrombosis (DVT)		
past history	5 (9%)	1 (2%)
present at screening	0	0
no	50 (91%)	55 (98%)
Pulmonary embolism		
past history	3 (5%)	0
present at screening	0	0
no	52 (95%)	56 (100%)
Renal dysfunction		
past history	2 (4%)	3 (5%)
present at screening	1 (2%)	0
no	52 (95%)	53 (95%)

reviewer's table, from sponsor's tables, NDA Vol. 30.3, pp. 105 through 108 and 131 through 139

Most patients had a scleroderma history of at least 5 years and had had pulmonary hypertension for at least 8 months. About 13% of patients had history of using anorexic agents in the past and these patients were about equally distributed between the two treatment groups. About 5% of patients had a history of thromboembolic disease and all but one of these patients was randomized to the conventional group. Dyspnea-fatigue Rating at baseline tended to be worse in the conventional treatment group while Borg Dyspnea score at baseline tended to be worse in the FLOLAN group.

All patients were on at least one medication at baseline and all patients except 1 patient in the conventional group were on some concomitant medication for at least 75% of the time on study. A tabulation of concomitant drug usage by organ system is shown below:

Study VA14A4001: Concomitant Medication Use by Organ System

	Number of Patients (%)			
	Baseline		During Study	
	Conventional (n=55)	FLOLAN (n=56)	Conventional (n=55)	FLOLAN (n=56)
Any Medication	55 (100%)	56 (100%)	54 (99%)	56 (100%)
Cardiovascular System	51 (93%)	52 (93%)	54 (98%)	55 (98%)
Drugs Acting via the Nervous System	43 (78%)	48 (86%)	39 (71%)	47 (84%)
Non-Drug Products	42 (76%)	38 (68%)	42 (76%)	38 (68%)
Endocrine and Metabolic	36 (65%)	37 (66%)	38 (69%)	35 (63%)
Gastrointestinal System	40 (73%)	32 (57%)	34 (62%)	37 (66%)
Nutrition	38 (69%)	33 (59%)	38 (69%)	33 (59%)
Anti-Infectives & Immunologicals	5 (9%)	21 (38%)	2 (4%)	9 (16%)
Various Drugs	6 (11%)	4 (7%)	7 (13%)	3 (5%)
Cytotoxics & Anti-Neoplastics	3 (5%)	2 (4%)	3 (5%)	1 (2%)
Skin, Ear & Eye Preparations	2 (4%)	3 (5%)	2 (4%)	5 (9%)

reviewer's table, based on sponsor's table, NDA Vol. 30.3, pp. 110 through 121

The following table lists medications that were used by 7 or more patients at baseline or during the study:

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ON ORIGINAL

Study VA14A4001: Most Frequently Used Concomitant Medications

	Number of Patients			
	Baseline		Used At Least 75% of Time During Study	
	Conventional (n=55)	FLOLAN (n=56)	Conventional (n=55)	FLOLAN (n=56)
Cardiovascular system:				
furosemide	30	31	30	32
warfarin sodium	27	20	37	48
digoxin	16	16	19	18
nifedipine	12	16	12	7
diltiazem hydrochloride	8	9	8	7
amlodipine	7	9	9	8
spironoloactone	6	5	9	7
oxpentifylline	3	6	3	4
lisinopril	4	4	4	2
metolazone	2	6	1	5
adenosine	2	5	0	1
enalapril maleate	6	1	4	0
heparin	1	6	0	1
torasemide	5	2	5	4
Drugs Acting via the Nervous System				
lignocaine	22	30	15	20
paracetamol	9	23	9	26
midazolam HCl	6	21	4	8
aspirin	10	4	8	4
diphenhydramine	5	7	0	4
alprazolam	5	6	5	4
diazepam	3	6	2	1
fentanyl	0	8	0	1
amitriptyline HCl	4	3	4	3
hydroxyzine	4	3	4	2
lorazepam	1	6	1	5
salbutamol sulfate	5	2	5	1
acetaminophen + codeine	0	6	1	2
fluoxetine HCl	2	4	3	4
propoxyphene napsylate + acetaminophen	3	3	4	3
sertraline HCl	2	3	2	5
Non-Drug Products				
oxygen	42	38	42	38
Endocrine & Metabolic				
prednisone	16	10	15	10
thyroxine sodium	10	15	10	14
conjugated estrogens	7	12	6	11
Gastrointestinal system				
omeprazole	20	17	20	14
cisapride	10	5	10	8
famotidine	5	6	5	4
ranitidine HCl	7	2	7	3
loperamide HCl	0	2	0	9
Nutrition				
potassium chloride	27	22	26	22
calcium salt	6	5	6	5
multiple vitamin	4	7	4	7
ferrous sulfate	7	1	8	3
vitamin E	5	2	4	3

reviewer's table, based on sponsor's table. NDA Vol. 30.3, pp. 110 through 121

There were generally more patients in the conventional therapy group who were on vasodilators prior to study and continued vasodilator therapy throughout the study: oxygen (65% of conventional, 57% of FLOLAN); calcium channel blockers (44% of conventional, 34% of FLOLAN); ACE inhibitors (16% of conventional, 5% of FLOLAN); nitro vasodilators (7% of conventional, 4% of